International Perspective
Working Group on Rare Blood Disorders, FVIII/IX Subcommittee, ISTH

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Rare Bleeding Disorders (RBDs)

- These disorders, inherited as autosomal recessive traits, are very rare with a prevalence of approx. 1:500,000 to 1:2,000,000 in the general population
- Recessive disorders are more prevalent in developing countries because of higher frequency of consanguineous marriages

  → frequencies similar to those of haemophilia B

  → there is a greater demand for diagnosis and treatment

Background

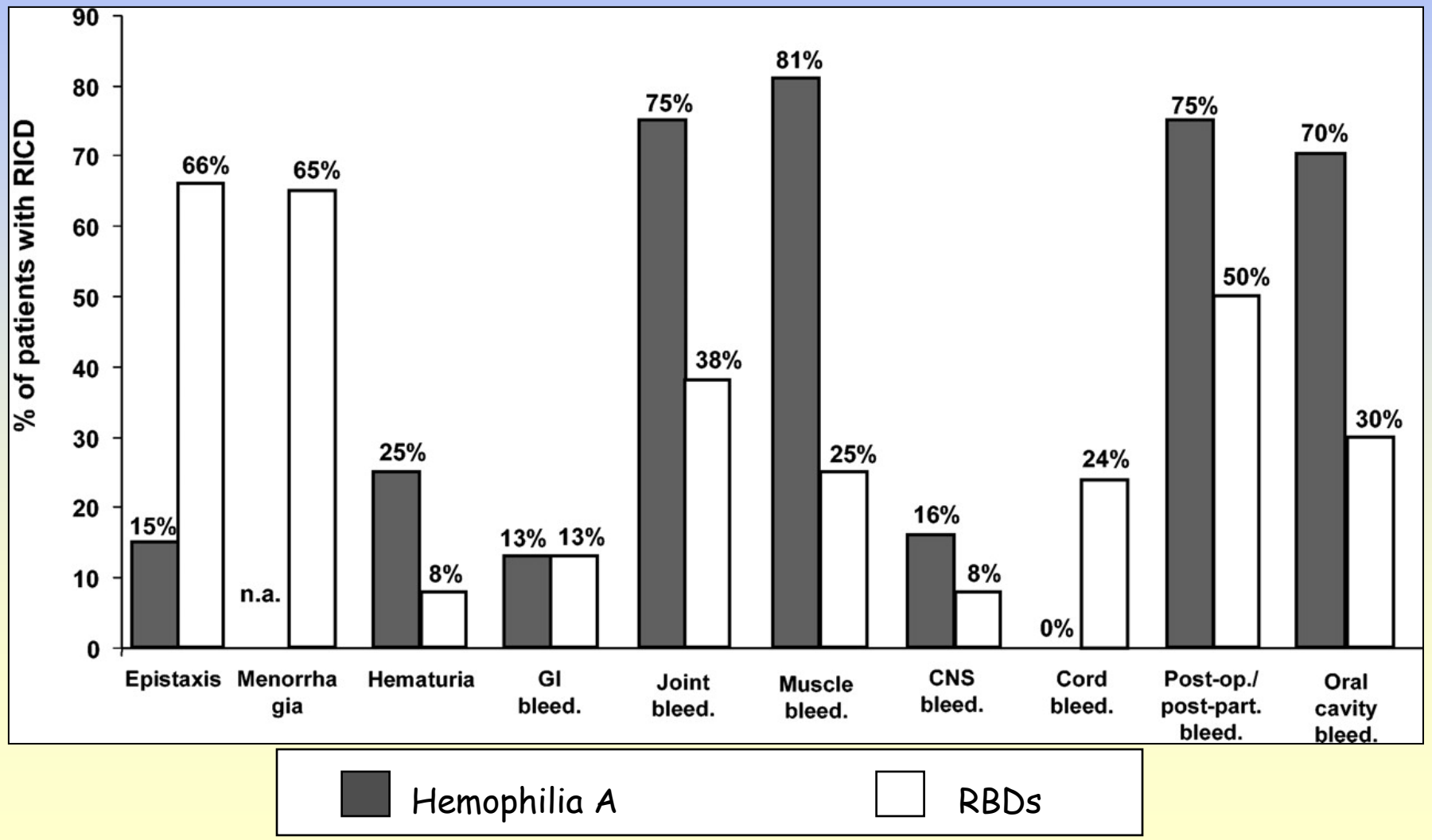
As a consequence of the relative rarity of these deficiencies are typically orphan diseases, relatively neglected until recently by health care providers, advocacy organizations and pharmaceutical companies

Clinical manifestations in RBDs

Less severe than hemophilia A and B

- life and limb threatening symptoms apparently less frequent
- varies from mild to moderate bleeding episodes to potentially serious or life threatening haemorrhages

Bleeding symptoms in RBDs patients vs Hemophilia A



Clinical manifestations-Italian cohort

FVIII		Fibrinogen	FII	FV	FVII	FV+FVIII	FX	FXI	FXIII
15%	Nose bleeding	70%	60%	57%	64%	77%	72%	34%	32%
0%	Uterus bleeding	50%	75%	50%	60%	58%	50%	8%	35%
25%	Hematuria	0%	7%	6%	10%	0%	25%	3%	10%
13%	GI bleeding	0%	15%	6%	14%	7%	38%	0%	10%
75%	Joint bleeding	50%	38%	26%	21%	25%	69%	29%	55%
81%	Muscle bleeding	0%	38%	29%	12%	7%	66%	32%	58%
16%	CNS bleeding	5%	7%	6%	17%	4%	9%	0%	25%
0%	Cord bleeding	75%	15%	3%	0%	22%	28%		73%
75%	Post- partum, -operation bleeding	40%	23%	43%	55%	0%	0%	63%	84%
90%	Oral cavity bleeding	70%	46%	57%	66%	51%	0%	55%	48%

Treatment in RBDs

- Since there are few long term prospective studies of large cohorts of patients, reliable information about clinical management is often scarce

- Coagulation factor support may require the prescription of unlicensed treatment products that are not readily available

  → purified factor concentrates are not as readily available as for haemophilias

Treatment in RBDs

- Replacement therapy
- Non-transfusional treatment

Replacement therapy (FFP)

- The backbone treatment is a single-donor **fresh-frozen plasma** (**FFP**):
  - containing all coagulation factors
  - relatively inexpensive and
  - widely available

- **Virus-inactivated FFP** preferable to plain FFP (metodi)

Replacement therapy (concentrates)

- A few single-factor, plasma-derived fibrinogen, FVII, FXI and FXIII concentrates differently licensed in some European countries and in the USA
- Prothrombin and FX deficiencies often treated with prothrombin complex concentrates (PCCs)
  - contain unnecessary amounts of vitamin K-dependent factors over the actually deficient ones

There was little progress in treatment! Only one recombinant DNA technology drug is available in Europe not in USA:

- rFVIIa licensed for FVII deficiency

FV and combined FV/VIII deficiencies can only be treated with fresh frozen plasma

Factor concentrates for RBDs

Coagulation factor (brand)	Manufacturer	Plasma Source	Export / Domestic	Fractionation	Viral inactivation	Comments
Fibrinogen (Haemocomplettan HS)	ZLB Behring, Marburg, Germany	USA, Austria, Germany; paid & unpaid	Both	Multiple precipitation	Pasteurization at 60°C, 20h	Albumin added
Fibrinogen (Clottagen)	LFB, Les Ulis, France	Western Europe, unpaid	Both	Cryoprecipitation, adsorption on aluminum hydroxide gel, anion exchange chromatography	TNBP/polysorbate80	—
Fibrinogen	SNBTS, Edinburgh,Scotland	USA, Germany; unpaid	Both	Multiple precipitation, ion exchange chromatography	TNBP/polysorbate8; dry heat, 80°C, 72h	No albumin added
Fibrinogen (Fibroraas)	RAAS, Shanghai, China	China; paid & unpaid	Both	Multiple fractionation	TNBP/polysorbate80	—
Fibrinogen HT	Benesis, Osaka, Japan	Japan; unpaid	Domestic	Ethanol fractionation, glycine precipitation	TNBP/polysorbate8; dry heat, 60°C, 72h; 35 nm nanofiltration	No albumin added
Factor VII	Bio Products Laboratory, Elstree, UK	USA; paid apheresis	Both	Ion exchange chromatography	Dry heat, 80°C, 72h	S.A. 1,5-2U/mg protein
Factor VII (Facteur VII)	LFB, Les Ulis, France	France; unpaid recovered & apheresis	Both	DEAE adsorption, anion exchange chromatography	TNBP/polysorbate80	S.A. 1-2U/mg protein. No albumin added
Factor VII (Provertin)	Baxter BioScience, Vienna, Austria	USA, Austria, Czech Rep, Germany, Sweden; mostly paid apheresis	Both	Alluminum hydroxide absorption	Vapor heat, 60°C, 10 h, at 190 mbar + 80°C, 1h, at 375 mbar	—
Factor XI	Bio Products Laboratory, Elstree, UK	USA; paid apheresis	Both	Affinity heparin sepharose chromatography	Dry heat, 80°C, 72h	Heparin and ATIII added. S.A. 3->5U/mg protein
Factor XI (Hemoleven)	LFB, Les Ulis, France	Western Europe; unpaid	Both	Dialysis, cation exchange chromatography	Solvent/detergent, 15 nm nanofiltration	Heparin, ATIII, and C-1 esterase inhibitor added
Factor XIII (Fibrogammin HS)	ZLB Behring, Marburg, Germany	USA, Austria, Germany; paid & unpaid	Both	Multiple precipitation	Pasteurization at 60°C, 10h	Albumin added

Prothrombin complex concentrates (PCC)

Coagulation factor (brand)	Manufacturer	Plasma Source	Export / Domestic	Fractionation	Viral inactivation	Comments
Proplex-T	Baxter BioScience, USA	USA; paid apheresis	Both	Ticalcium phosphate absorption, PEG fractionation	Exposure to 20% ethanol; dry heat	Heparin added
Prothroraas	Shangahi RAAS, China	China; paid & unpaid apheresis	Both	PEG precipitation, DEAE-sephadex	S/D nanofiltration	-
Beriplex P/N	ZLB Behring, Germany	USA, Austria, Germany; paid & unpaid	Both	DEAE-sephadex	Pasteurization and nanofiltration	ATIII, Heparin & Albumin added
Faktor IX HS	ZLB Behring, Germany	USA, Austria, Germany; paid & unpaid	Both	DEAE-sephadex	Pasteurization and nanofiltration	Contains high amount of FX
Haemosolvex Factor IX	Natal Bioproducts, South Africa	South Africa; unpaid	Both	DEAE-sephadex	TNBP/polysorbate80	No Albumin added
Profilnine SD	Grifols, USA	USA; paid pheresis	Both	DEAE-cellulose adsorption	TNBP/polysorbate80	ATIII, Heparin added; No albumin
Prothrombinex/HT	CSL Ltd, Australia	Australia, New Zeland, Hong Kong, Malaysia; unpaid	Both	DEAE-cellulose adsorption	Dry heat	ATIII, Heparin added; No albumin
Prothromplex/T	Baxter BioScience, Austria	USA, Austria, Czech Rep, Germany, Sweden; mostly paid apheresis	Both	Ion-exchange adsorption	Vapor heat, at 190mbar, then at 375mbar	ATIII, Heparin added
Bebulin VH	Baxter BioScience, Austria	USA; paid apheresis	Export to USA	Ion-exchange adsorption	Vapor heat, at 190 mbar then at 375 mbar	Heparin added
HTDEFIX	SNBTS, Scotland	USA, Germany; unpaid	Both	Ion-exchange chromatography	Dry heat,	Heparin and ATIII added.
Facnyne	GreenCross PD, Korea	Korea; unpaid	Domestic	Ion-exchange chromatography	TNBP/polysorbate80	No Albumin added
Cofact	Sanquin, Netherlands	Netherlands; unpaid	Both	DEAE ion-exchange chromatography	TNBP/polysorbate80, nanofiltration	ATIII adeed
PPSB-Human SD/Nano 300/600	German Red Cross NSTOB, Germany	Germany; unpaid	Domestic	DEAE-sephadex ion-exchange chrom.	TNBP/polysorbate80, 2 nanofiltration steps	ATIII and Heparin added, No Albumin
UMAN Complex D.I.	Kedrion, Italy	Europe & USA; paid & unpaid	Both	DEAE-sephadex/ sepharose chromatography	TNBP/polysorbate80, dry heat	ATIII and Heparin added, No Albumin. FII and FX titration
KASKADIL	LFB, France	Western Europe; unpaid	Both	DEAE-sephadex adsorption, anion-exchange cromatog	TNBP/polysorbate80	-

World Federation of Hemophilia, 2005

Available products...

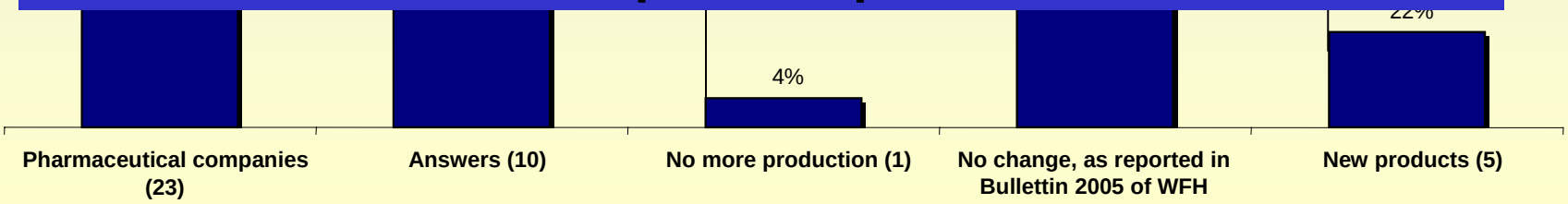
Questionnaire containing the following questions was sent to 23 manufacturers:

- Which products do you produce that you think could be useful in rare bleeding disorders treatment?
- Are there any variations in the production of your new products?
- Are they plasma derived?
- Which virus inactivation method do you use?
- Have you add any step on virus activation on your product?
- In which type of rare bleeding disorder are they usually used?
- In which region of the world are they usually distributed?

10/23 manufacturers answered...

Only 1 new product for fibrinogen deficiency emerged from the questionnaire

→The trend of farmaceutical manifacture research is principally focused on new products to treat Haemophilic patients



Recombinant FXIII (ZymoGenetics, Inc.)

T. C. Reynolds, *et al*. JTH 2005; 3:922-8

- A recombinant human FXIII (rFXIII) A2 homodimer, equivalent to cellular FXIII normally found in platelets, was produced in the yeast Saccharomyces cerevisiae
- A clinical study was designed and performed to evaluate the safety, pharmacokinetics, and immunogenicity of recombinant FXIII (rFXIII) administration to 50 healthy adult volunteers
- Recombinant FXIII was well tolerated, with no serious adverse events or dose related toxicities
- Increase in circulating A2B2 and decrease in free FXIII-B subunit indicate in vivo formation of FXIII heterotetramer
- Safety, pharmacological and immunological profile of rFXIII suggests it should be studied in patients with congenital FXIII subunit A deficiency as well as evaluated as a systemic hemostat in patients with acquired FXIII deficiency or hemorrhage

Available Guidelines for RBDs treatment

- PM Mannucci et al, Blood, 2004

"Recessively inherited coagulation disorders"

- PHB Bolton-Maggs et al, Haemophilia 2004

"The rare coagulation disorders –review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation"

but still there are different open questions which needs to be answered?

Working group of RBDs (ISTH)

- To constantly follow (overhaul) drug production, cost and distribution in the World
- To tailor treatment guidelines to each particular deficiency (on demand or prophylaxis cases)
- To target guidelines to children/adults and pregnant women specifically
- To consider primary prophylaxis in heterozygous patients especially regarding major surgical interventions
- To evaluate the use of prothrombin complex in view of possible thrombotic complications in patients with a vit.K dependent protein deficiency